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USSR WORK ON THE PHYSIOLOGICAL ASPECTS OF INFECTION PROCESSES

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A number of observations and experiments involving the application of prolonged drug-induced sleep which were conducted on rabbits and simians by I. Ya. Uchitel' at the Institute of Surgery imeni A. V. Vishnevskiy, Academy of Medical Sciences USSR, have demonstrated that an indispensible condition for the origination of an infectious-toxic process is the existence of a definite level of irritability (reactivity) of tissues within the organism at the time when the biological agent in question exerts its effect. In the final count, this condition determines the susceptibility of the organism to the infection of intoxication in question.

An artificial modification of the reactivity of the organism enables us either to reinforce the infectious-toxic processes or to prevent them partially or entirely. For instance, when animals are in a state of profound sleep produced by drugs, one cannot reproduce local infectious-toxic and allergic reactions affecting the skin or the joints. This can be readily understood if we take into consideration that the processes of inhabition which form the basis of sleep exculde exteroreception and proprioreception. On the contrary, in accordance with the fact that interoreception is not eliminated in drug-induced sleep, but perhaps even strengthened, the state of sleep not only does not prevent, but rather strengthens the infectious-toxic and allergic processes which occur in internal organs and tissues.

To understand the phenomena described, one must note that whenever the occurrence of infectious-inflammatory reactions is prevented on the skin or in the joints under the influence of sleep, the causative factor is nevertheless preserved and may induce the reaction which is typical for it after the culmination of sleep. This, in turn, emphasizes in a striking manner the decisive importance of the irritability of the tissues and organs involved with reference to the biological agent in question, in determining whether or not the process of infection will be induced.

The relationships which have been indicated and which have a bearing on the origination of infectious-toxic and allergic processes depend on the state of activity of the organs and tissues affected. This is illustrated in Uchitel's experiments by many observations dealing with the reproduction in sleeping animals of various types of local and general effects of different vaccines (diptheria, staphylococci, and tetanus vaccines) and of living causative factors, (straphylococci, the virus of vaccinia, and the virus of rabies).

All this makes it possible to assume that the basis of the so-called tissue immunity which has been acquired is formed by a loss on the part of the organism of the reactivity of the tissues in question toward the infectious toxic agent. The cause of this lies in the hyperirritation of tissues by this agent during the process of infection or of immunization, so that a state of inhibition inevitably arises. Thus, the third factor of immunity, as Prof A. T. Kravchenko has called tissue immunity, becomes identical from this standpoint with the nonreactivity of tissues resulting from the development of a state of inhibition.

This interpretation of the processes of infection and tissue immunity brings out with great clarity the significance of the nervous system, which in the last account regulates the reactivity of cell elements by exerting

an active effect on the level of irritability possessed by them. The regularities governing excitation and inhibition also fully explain the humoral manifestations of immunity, which are reflected in the production of specific antibodies and also in various allergic reactions and reactions similar to them.

It is generally known that under the action of an antigen, an increased irritability (reactivity) towards the antigen arises in the organism. Under the repeated action of the same antigen reinforced and accelerated production of the antibodies in question takes place. Furthermore, an increased tendency toward various allergic reactions develops.

At the same time, there is in the immunologically modified organism which has been altered both with respect to the production of antibodies and the reproduction of allergic reactions, a variety of inhibition processes similar to those which occur in systems that can be stimulated [i. e., nonimmunized systems]. In accordance with the general postulate of N. Ye. Vvedenskiy in regard to the coupling between irritation and inhibition in immunologically highly-reactive animals, subsequently to a very active production of antibodies under the influence of revaccination, a refractory condition with respect to the identical irritant, i. e., the antigen, invariably arises.

Similarly, in sensitized animals after an anaphylactic shock, an analogous state of refractoriness or of antianaphylaxis ensues.

When animals are highly reactive to two antigens, complete inhibition toward the action of one of them arises when there is hyperirritation due to the action of the other. According to K. P. Chepalov, reproduction of an excessively strong allergic reaction (para-allergic reaction), for instance in a lung, may completely inhibit a less strongly pronounced reaction of the same type on the skin.

Finally, the production of antibodies and the development of allergic reactions may be completely or parially suppressed under the effect of sleep inhibition achieved in the state of drug-induced sleep. The rule of the additivity of irritations is fully applicable to infectious-toxic processes, particularly as far as the additivity of effects produced by subthreshold doses of toxic bacterial products and allergens is concerned. The phenomena of the additivity of specific irritations produced by infectious -- toxic products and allergens undoubtedly play a prominent role in the pahtogenesis of infections and intoxications. It is possible that these phenomena determine the length of the incubation period in infectious diseases. The role of the additivity of irritations fully explains the action on the organism of antigens which are repeatedly administered for the purpose of immunization with short intervals between the administrations. Thus, the regularities governing irritation, inhibition, and the addition of irritations which have been established by the founders of our national physiology, I. M. Sechenov, I. P. Pavlov, and N. Ye. Vvedenskiy, are fully applicable to the processes of infection and immunity.

Where are the processes of irritation and inhibition and those based on the additivity of irritations localized and how do they progress during the development of infection and immunity? It is obvious that the phenomena in question takes place in the cells of the tissues involved. Specifically, in connection with the production of immune antibodies, they take place in the cells of the reticuloendothelial system and the lymphoid tissue.

In discussing this question, one must consider the possibility and obvious nature of the direct action of bacterial irritants on the cells involved as well as the possibility and probability of independent reactions of cells towards the action of bacterial irritants. The assumptions that have been made

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are in accordance with the pronouncement of N. Ye. Vvedenskiy to the effect that the peripheral systems which are regulated by the central nervous system are not as such completely passive and indifferent tools, but live a life of their own and possess an independent reactivity, although this reactivity may be less than that of nerve tissue. This idea is confirmed by the prominent electrophysiologist A. F. Samoylov, who in his article on parabiosis (1931) states: "Not only a nerve but any formation that is susceptible to stimulation may fall into the state of parabiosis. "This means that any cell, generally speaking, may fall into the state of parabiosis, because susceptibility to stimulation is the basic property of any kind of living cytoplasm.

One must take into consideration in connection with this that the processes of infection and immunization are under the influence of the nervous system, which regulates the level of the irritability of cell elements and apparently exerts an action on them that is important from the standpoint of adaptation and trophism. This applies first of all to the cells which produce immune antibodies in as far as the formation of antibodies is connected with the synthesis of globulins that are modified under the influence of the antigen resorbed by reticuloendothelial cells.

Let us now discuss the problem ofthe influence of nerve reflex mechanisms on the pathogenesis of infections and immunogenesis.

Numerous experiments carried out at our laboratory by G. V. Shumakova with different experimental models using rabbits for this purpose did not confirm, in contradistinction to former observations made by V. M. Aristovskiy, that specific irritations may be transmitted along nerve paths subsequently to the action of tetanus toxin or tetanus anatoxin on the reception apparatus or stump of a severed sciatic nerve (this is the technique formerly used by Aristovskiy). Neither a tetanus syndrome nor the development of antitoxin on revaccination could be reproduced in the animals. In other words, these phenomena could not be reproduced under the optimal conditions as far as reactivity of the animal is concerned. Similar negative results were obtained by other investigators (N. V. Golikov, 1949, L. N. Fontalin, 1953; etc.). It became clear in Shumakova's experiments that even the action of subminimal doses of toxins on the corresponding reflexogenic zones may reproduce as a reflex nonspecific afflications of organs. These afflications preserve a sterotyped character and do not depend on the kind of toxin which is used. For instance, a typical pulmonary syndrome could be regularly reproduced in rabbits. This syndrome culminated in the death of the animals on the 4th and 5th day, when an acute affection of the lungs developed after subminimal doses of tetanus toxin, dysentery toxin, or another toxin had been introduced into the reflexogenic zone of the carotid sinus. This nonspecific syndrome can be prevented only by rigid specific immunization against the particular kind of toxin used as an irritant.

Experiments by A. A. Klimentova and G. V. Shumakova have also shown that nonspecific irritants may produce as a reflex anamnestic reactions in previously immunized animals. These reactions are accompanied by the appearance of antibodies in the blood or an increased titer of the antibodies in the blood.

Under the conditions described, application of an irritant of sufficient strength (for instance, of electrical stimulation to the skin) may increase the titer of antibodies by a factor of 6-10 as compared with the initial titer.

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Thus the microorganisms which function as causative factors and the metabolic products of these microorganisms may produce in the body reflex reactions which have a considerable pathogenetic significance. However, these reactions are unspecific and bear a stereotyped character. Nevertheless, irritants of various types may produce as reflexes definite effects on the production or the distribution of immune antibodies, even though the immunological effects thus produced must be regarded as unspecific phenomena.

The contradictory nature and methodological incompleteness of observations concerning the effect of conditioned reflexes on the production of immune antibodies made it necessary to conduct during the period 1951-1953 in our laboratory at the Institute of Physiology, Academy of Medical Sciences USSR, a considerable number of observations in this field. A. A. Klimentova, G. V. Shumakova, Ye. A. Yakovleva, and V. A. Katsitadze participated in the work in question, in the course of which 184 experiments were carried out. The effects of conditioned reflexes on the production of agglutinins and antitoxins were studied. In the experiments in question, 12 qualitatively distinct, simple and complex, conditioned irritants were used. The irritants were applied during periods ranging from several minutes or seconds to 2-10 hours; the number of combinations ranged from 9-10 to 15-25. However, the general result of the experiments must be regarded as negative.

Thus, according to our data, reproduction of the development of immune antibodies by means of conditioned reflexes is a goal which must be regarded as unrealistic. Work on this subject cannot be expected to bear practical results.

Our conclusions regarding the applicability of some physiological rules to the processes of infection and of immunogenesis represent the first stage of phenomenological generalizations in this field. Further study of the relationships involved must be carried out on the basis of the exact methods of biochemistry and biophysics, including cytomorphology. Soviet immunology must pay particular attention to the achievements of immunochemistry, utilizing first of all the most effective methods in this field which involve application of antibodies (i. e., globulins) containing tracer atoms and also of antigens containing such atoms.

Accordingly, a department of theoretical immunology and an immunochemical laboratory attached to this department must be created within the system of institutes of the Academy of Medical Sciences USSR.

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